Synthesis of Natural Products By Rhodium-Mediated Intramolecular C–H Insertion

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Abstract: Rh-mediated intramolecular C–H insertion allows the direct construction of carbon–carbon bonds at previously unactivated centers. The natural product syntheses described here highlight the strategic advantages and efficiencies this reaction offers.

Keywords: C–C coupling · cyclizations · diazo compounds · natural products · rhodium

Introduction

Since the observation that Rh^{II} carboxylates are superior catalysts for the generation of transient electrophilic metal carbenoids from α-diazocarbonyl compounds, intramolecular carbenoid insertion reactions have assumed strategic importance for C–C bond construction in organic synthesis.[1] Rhodium(II) compounds catalyse the remote functionalization of carbon–hydrogen bonds to form carbon–carbon bonds with good yield and selectivity. These reactions have been particularly useful in the intramolecular sense to produce preferentially five-membered rings. We summarize here the applications of this method for ring construction in natural product synthesis.

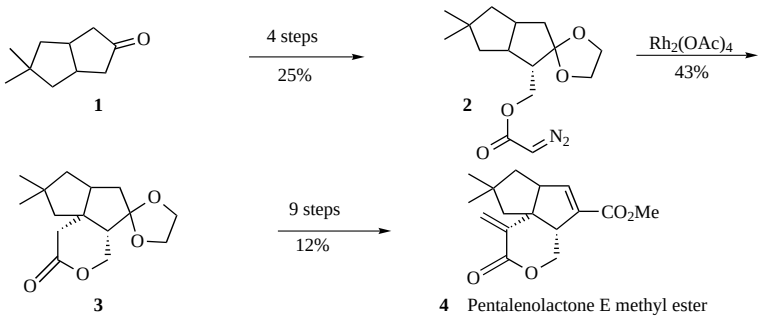
Discussion

Although most of the work with Rh-mediated intramolecular C–H insertion has focused on five-membered ring construction, the first application to natural product synthesis, by Cane and Thomas, involved establishment of a six-membered ring. Thus, on exposure to $[Rh_2(OAc)_4]$, diazoketone **2** was cyclized to the tricyclic lactone **3**.[2] This product had previously been transformed by Paquette et al. into pentalenolactone E (**4**, Scheme 1).[3]

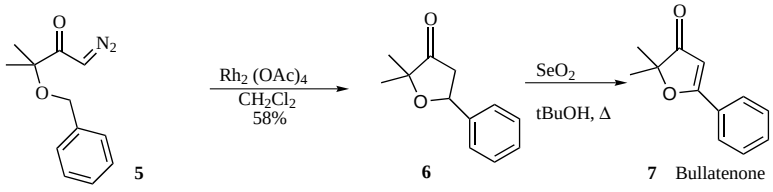
The utility of this approach to five-membered *heterocycles* is illustrated by the synthesis of bullatenone (**7**) by Adams et al. (Scheme 2). Rhodium-acetate-mediated insertion is especially preferred adjacent to ether oxygen, as illustrated by the cyclization of **5** to **6**.[4] Oxidation of furanone **6** with SeO_2 according to the procedure of Smith and Jerris provided bullatenone (**7**).[5]

Rh-mediated C–H insertion is also useful for *carbocyclic* construction, as illustrated by the new asymmetric route to (+)-morphine (**11**) recently reported by White et al. (Scheme 3).[6] Cyclopentane formation is used to fashion a pentacyclic skeleton (**10**) from which the piperidine ring of **11** evolves at a later stage.

Intramolecular C–H insertion is, essentially, a method for the specific remote functionalization of hydrocarbons. An important implication of this for synthetic strategy is that the C–H insertion process can destroy symmetry, thus leading



Scheme 1. Formation of a six-membered ring by Rh-mediated intramolecular C–H insertion.



Scheme 2. Formation of a five-membered heterocycle in Adams' synthesis of bullatenone.

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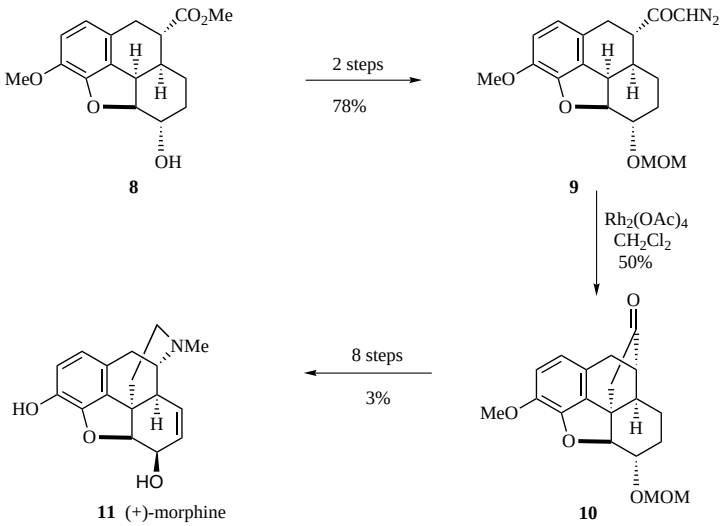
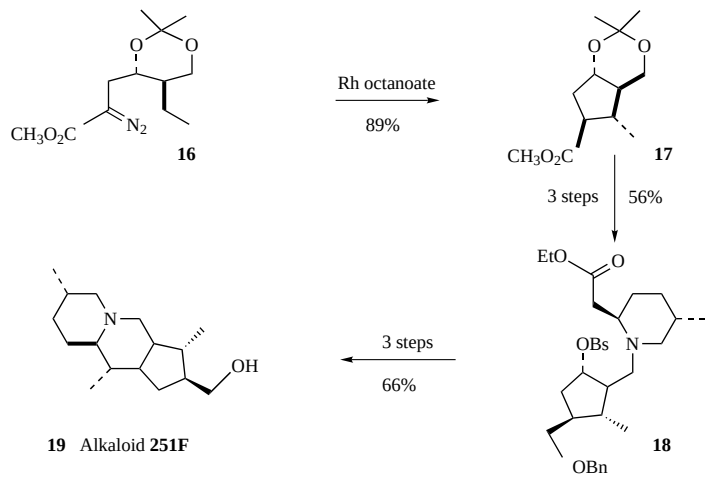


Scheme 3. Carbocycle construction by Rh-mediated C–H insertion to give (+)-morphine.

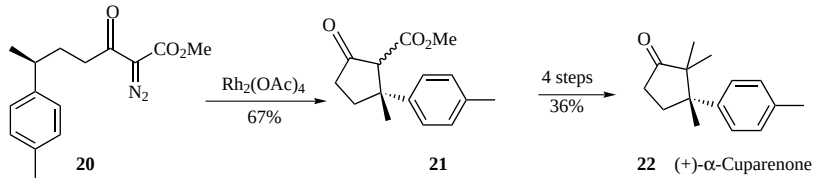


Scheme 5. A simple route to the dendrobatid alkaloid 251F.

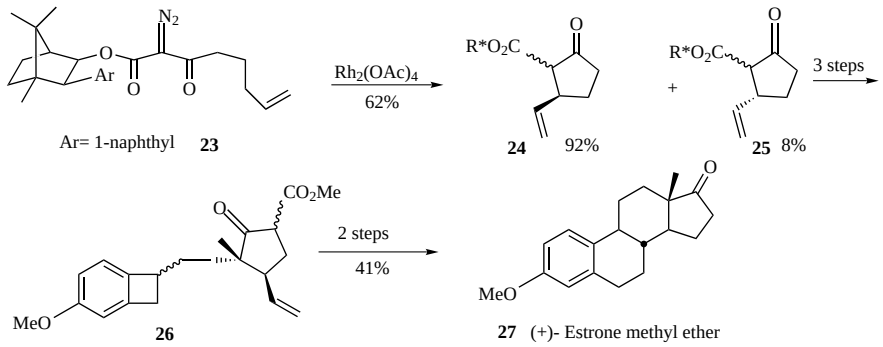
from a simple precursor to a much more complex product. An alternative route to pentalenolactone E (**4** or **15**) takes advantage of this idea.[7] In the key step β-ketoester **13**, which has a single stereogenic center, is transformed into the tricycle **14**, which has four stereogenic centers (Scheme 4).

A simple route to the dendrobatid alkaloid 251F (**19**, Scheme 5) nicely illustrates the synthetic utility of Rh-mediated C–H insertion.[8] The excellent diastereoselectivity observed in the cyclization of **16** to **17** was in fact predicted computationally.[9]

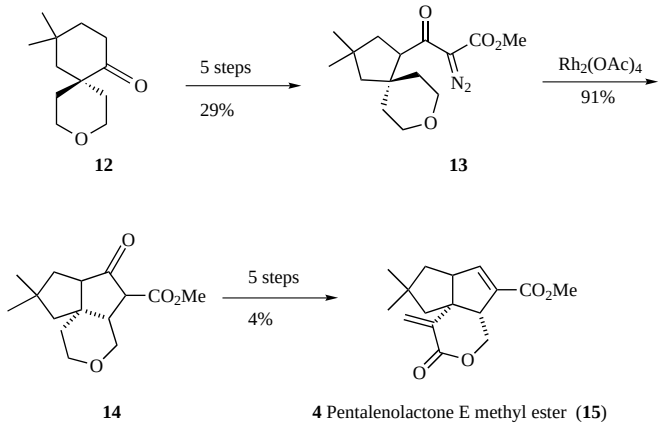
A key feature of intramolecular C–H insertion is the inherent ability to transform an acyclic tertiary stereogenic center into a cyclic quaternary stereogenic center, with retention of absolute configuration.[10] This was first demonstrated in the course of the rhodium-mediated cyclization of **20** to **21** shown in Scheme 6, which led to (+)-α-cuparenone (**22**).[11]



Scheme 6. The transformation of an acyclic tertiary stereogenic center into a cyclic quaternary stereogenic center with retention of absolute configuration illustrated by the synthesis of (+)-α-cuparenone.



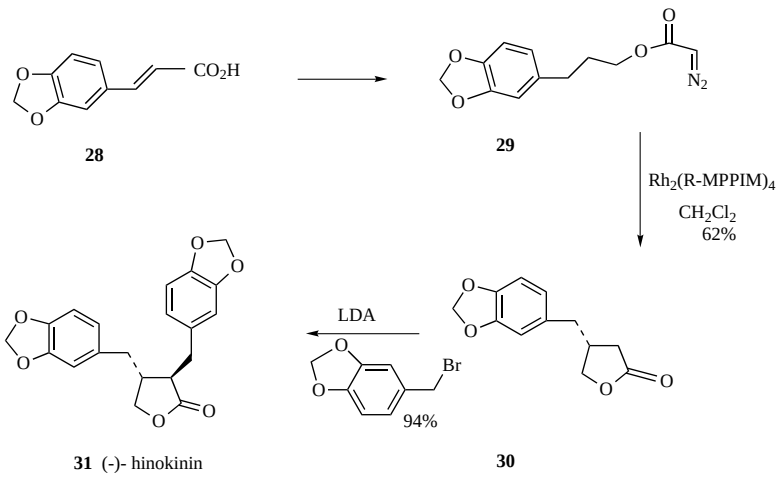
Scheme 7. Directed Rh-mediated intramolecular C–H insertion.



Scheme 4. From a simple precursor to a much more complex product, pentalenolactone E methyl ester.

The synthesis of (+)-estrone methyl ether (**27**) illustrates the enantioselective construction of a polycyclic target using chiral auxiliary control to establish the first cyclic stereogenic center.[12] The specific design of the naphthyl diazoester **23** directs Rh-mediated intramolecular C–H insertion selectively toward one of the two diastereotopic C–H bonds on the target methylene. The new ternary center so created then directs the formation of the adjacent quaternary center in the course of the alkylation. The chiral skew in the product cyclopentanone **24** directs the relative and absolute course of the intramolecular cycloaddition, to give the steroid (+)-estrone methyl ether (**27**).

The high point in the development to date of Rh-mediated C–H insertion has been the design by Doyle et al. of enantiomerically pure Rh^{II} complexes that direct the absolute sense of the C–H insertion reactions. The application of



Scheme 8. Direction of the absolute sense of C–H insertion by enantiomerically pure Rh^{II} complexes, illustrated by the construction of (−)-hinokinin.

such cyclizations in natural product synthesis was demonstrated by Doyle with the construction of chiral lignan lactones such as (−)-hinokinin (**31**, Scheme 8).[13]

The α-diazocarbonyl derivatives used in these studies are easily prepared, and the rhodium-mediated cyclizations proceed rapidly, with high catalyst turnover. As the factors governing regio-, chemo-, diastereo- and enantioselectivity come to be better understood, the Rh-mediated cyclization of an α-diazocarbonyl derivative will come to be a powerful tool for natural product synthesis.

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[1] Reviews: a) A. Padwa, D. J. Austin, *Angew. Chem.* **1994**, *106*, 1881; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797; b) M. A. McKervey, T. Ye, *Chem. Rev.* **1994**, *94*, 1091; M. A. McKervey, M. P. Doyle, *Chem. Commun.* **1997**, 983; c) M. P. Doyle in *Homogeneous Transition-Metal Catalysts in Organic Synthesis* (Eds.: W. R. Moser, D. W. Slocum), ACS Advanced Chemistry Series 230, American Chemical Society, Washington (DC), **1992**, ch. 30; d) D. F. Taber in *Comprehensive Organic Synthesis*, *Vol. 3* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p. 1045; e) M. P. Doyle, A. B. Dyatkin, G. H. P. Roos, F. Ganas, D. A. Pierson, A. van Basten, P. Muller, P. Polleux, *J. Am. Chem. Soc.* **1994**, *116*, 4507; f) P. Wang, J. Adams, *J. Am. Chem. Soc.* **1994**, *116*, 3296; g) D. F. Taber in *Methods of Organic Chemistry (Houben-Weyl)* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, Vol. E21, p. 1127; g) for a recent review of intramolecular C–H insertion by *alkenylidenes*, see W. Kirmse, *Angew. Chem.* **1997**, *109*, 1212; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1164.
[2] D. E. Cane, P. J. Thomas, *J. Am. Chem. Soc.* **1984**, *106*, 5295.
[3] L. A. Paquette, G. D. Annis, H. Schostarez, J. F. Blount, *J. Org. Chem.* **1981**, *46*, 3768.
[4] J. Adams, M.-A. Poupart, L. G. Chris, *Tetrahedron Lett.* **1989**, *30*, 1749.
[5] A. B. Smith III, P. Jerris, *Synth. Commun.* **1978**, *8*, 421.
[6] J. D. White, P. Hrnciar, F. Stappenbeck, *J. Org. Chem.* **1997**, 62, 5250.
[7] D. F. Taber, J. L. Schuchardt, *J. Am. Chem.* Soc. **1985**, 107, 5289.
[8] D. F. Taber, K. K. You, *J. Am. Chem. Soc.* **1995**, *117*, 5757.
[9] D. F. Taber, K. K. You, A. L. Rheingold, *J. Am. Chem. Soc.* **1996**, *118*, 547.
[10] J. C. Gilbert, D. H. Giamalva, M. E. Baze, *J. Org. Chem.* **1985**, *50*, 2557.
[11] D. F. Taber, E. M. Petty, K. Raman, *J. Am. Chem.* Soc. **1985**, *107*, 196.
[12] D. F. Taber, K. Raman, M. D. Gaul, *J. Org. Chem.* **1987**, *52*, 28.
[13] J. W. Bode, M. P. Doyle, M. N. Protopopova, Q.-L. Zhou, *J. Org. Chem.* **1996**, *61*, 9146.

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